

Better Detection of Residual Disease and Prediction of AML Relapse

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Acute myeloid leukemia (AML) is a cancer of immature white blood cells of the myeloid line, which accumulate in the bone marrow and interfere with normal blood cell development. Chemotherapy is given over several induction phases to reduce or eliminate the cancer cells, called blasts. When the frequency of bone marrow blasts has been reduced to less than 5%, the disease is considered to be in complete remission. Although remission rates are quite high for young adults (up to 80%), only 30-40% of patients survive more than five years following diagnosis. Many patients succumb to disease relapse due to the presence of a small number of blasts that remain following chemotherapy and continue to grow. Current monitoring methods use microscopic analysis of blast size, shape and granularity, but may miss rare cells or those without grossly different morphology.

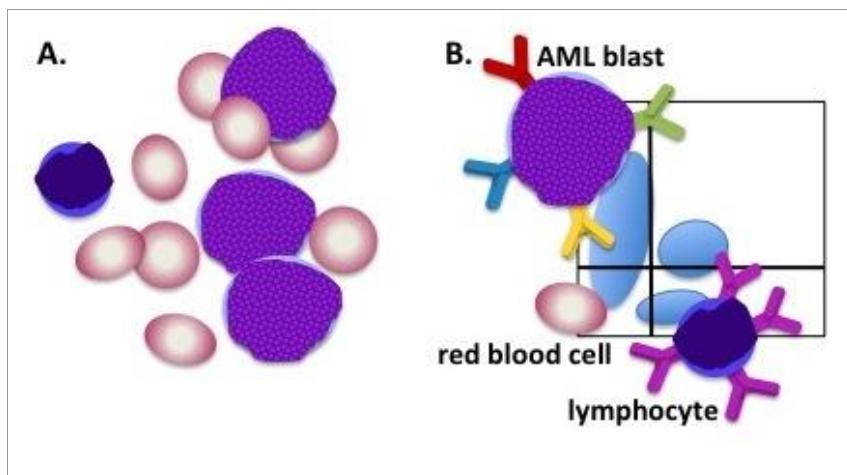
The presence of low-frequency cancer cells following chemotherapy, termed minimal residual disease (MRD), has been associated with an increased risk of relapse and poorer prognosis. Recent studies have focused on new and more sensitive methods to detect MRD, including the use of flow cytometry, which is a quantitative technique capable of rapidly detecting several surface and intracellular protein biomarkers that are present on millions of individual cells. The Clinical Research Division's Dr. Soheil Meshinchi and colleagues now report on the use of a flow cytometry-based panel of 15 biomarkers to detect MRD in 340 children and young adults with AML. Use of this multidimensional flow cytometry panel to detect aberrant expression of surface biomarkers on AML blasts allowed the authors to identify residual disease in more patients than was detected using standard morphological characterization. Furthermore, the presence of MRD in patients strongly correlated with disease outcome and provided prognostic significance.

Following induction chemotherapy, MRD was detected using standard morphological analysis and the cytometry biomarker panel. By morphology, 86% of patients were in complete remission (*i.e.* less than 5% blasts) after the first round of chemotherapy, which increased to 95% after a second round. The remaining patients had refractory or progressive disease, or were un-evaluable. The cytometry-based panel detected MRD in 31% of all patients, with blast levels ranging from 0.02% to 85% of bone marrow (median 2%). Of the 86% of patients considered in complete remission following the first round of chemotherapy, 25% had detectable blasts using the cytometry panel.

Dr. Meshinchi *et al.* then examined relapse and survival outcomes associated with MRD to determine the clinical implications of this new, more sensitive detection method. The risk of relapse among patients who were morphologically in complete remission but had detectable MRD by cytometry was 60%, more than twice that of patients with no detectable residual disease. Similar results were seen following a second round of chemotherapy, and for disease-free and overall survival. Among patients with more than 5% blasts by morphological assessment, 74% were MRD positive and had a three-year survival rate of 35%. The remaining patients for whom the cytometry panel did not detect residual disease were all long-term survivors, suggesting that the cytometry panel also identifies patients with good prognosis. Genetic and molecular factors, such as the mutational status of specific genes or chromosome losses, can also categorize AML patients into distinct subgroups with unique relapse risks. However, a large number of patients lack any type of prognostic factors, for which this cytometry panel may be particularly useful. For all subgroups, including those deemed to have favorable, standard or high-risk disease features, presence of residual disease was highly correlated with poorer outcomes.

The use of this cytometry biomarker panel will improve detection of residual disease and the allocation of additional therapies to patients. Patients with residual disease are likely to benefit from alternate therapies that are more intense, targeted or different formulations, whereas patients with undetectable disease may endure fewer or less intense treatments.

[Loken MR, Alonso TA, Pardo L, Gerbing RB, Raimondi SC, Hirsch BA, Ho PA, Franklin J, Cooper TM, Gamis AS, Meshinchi S.](#) 2012. Residual disease detected by multidimensional flow cytometry signifies high relapse risk in patients with *de novo* acute myeloid leukemia: a report from Children's Oncology Group. *Blood*. DOI: 10.1182/blood-2012-02-408336.



The use of flow cytometry to detect residual disease following chemotherapy improved the identification of patients with poor prognostic outcomes. A) Previously, morphological assessment of bone marrow was used to detect residual blasts based on shape and staining characteristics. B) New multidimensional flow cytometry uses a panel of 15 markers to label surface proteins on AML blasts and normal bone marrow cells. Based on these markers, cell size and granularity, residual AML blasts are better detected and indicate patients who may need additional treatment.